REMARKS

Response to Restriction Requirement

Applicants acknowledge the withdrawal of non-elected claims 45-49, 68 and 71-73 from consideration, with the intent to rejoin these claims when the composition claims are found allowable. Consistent with such intent to rejoin, applicants have amended the method claims, notwithstanding the Office's withdrawal of such claims, to present them in form suitable for future examination upon their rejoinder with the allowed elected claims.

Submission of Formal Drawings

Applicants submit herewith a set of formal drawings that meet all requirements of 37 C.F.R. 1.84.

Rejections of Claims and Traversal Thereof

In the November 27, 2002 Office Action,

claims 40, 42-44, 82 and 84-86 were rejected under 35 U.S.C. §112, second paragraph;

claims 40, 42-44, 82 and 84-86 were rejected under 35 U.S.C. §101; and

claims 40, 42-44, 82 and 84-86 were rejected under 35 U.S.C. §112, first paragraph.

The rejection of claims 40, 42-44, 82 and 84-86 is hereby traversed, and reconsideration of the patentability of amended claims 40, 42-44, 82 and 84-86 is requested, in light of the ensuing remarks.

Rejection under 35 U.S.C. §112, second paragraph

Claims 40, 42-44 and 82-86 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. According to the Office, the meaning of the term "native" is not clear. Applicants have provided a meaning for the term "native" at page 44 of the present specification. Specifically, the term "native" is defined as "derived from a naturally occurring source of hCG or β-hCG and not recombinantly

produced hCG or β-hCG." Examples of the different sources for hCG are discussed in the specification at page 77, in the last full paragraph, wherein the applicants describe that sources may include commercial hCG preparation, human pregnancy urine, urine from proteinuria patients, urine from patients with hCG secreting tumors and pituitary glands. Applicants believe there is ample description in the specification for one skilled in the art to understand the meaning of the term "native," however, to move the prosecution of this application forward, applicants have amended the claims to use the terminology "naturally occurring."

Further, applicants submit that the present specification provides ample guidance to determine the meaning of the terminology "has not been purified to homogeneity." Specifically, at page 151 of the specification, applicants discuss that the native hCG and native β-chain preparations "are not homogenous." Clearly, the terminology describes a sample, such as urine or a commercial product comprising urine that is not purified to a point wherein the sample must contain only one of the proteins. Further, as discussed at the top of page 152 of the specification, applicants state that "depending on the exact timing in the pregnancy, the urine sample may contain more or less of the free β-chain." Thus, the fractions that are prepared according to the methods set forth at page 166, whether a commercial sample of hCG or human early pregnancy urine, may contain some free β-chains and the present invention does not require the level of purification to remove these free β-chains from fractions after elution from the chromatography column.

Applicants submit that the definiteness of the language employed must be analyzed - not in a vacuum, but always in light of the teaching of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. The operative standard for determining if claims satisfy the requirement of §112 is whether those skilled in the art would understand what is claimed when the claims are read in light of the specification. Applicants' claims meet this standard. Accordingly, applicants respectfully request this rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Rejection under 35 U.S.C. §101/§112, first paragraph

Claims 40, 42-44, 82 and 84-86 were rejected under 35 USC §101/§112, first paragraph because the Office contends that the claimed invention is not supported by either a credible asserted utility or a well established utility, and as such, one would not know how to use the claimed invention. In response, applicants have amended the independent claims to read as follows:

1. A therapeutic composition for treating the **effects of HIV infection** comprising at least one fraction separated from a sample comprising urine which comprises naturally occurring hCG and/or β-hCG, wherein the at least one fraction comprises naturally occurring hCG and/or β-hCG and has an approximate molecular weight selected from the group consisting of 40 kD, 15 kD and 3 kD as determined by elution from a gel filtration sizing column relative to the elution of a naturally occurring hCG heterodimer with a molecular weight of 77 kD, and a β-hCG core protein or peptide with a molecular weight of 10 kD.

Applicants have shown in the testing procedures and results as set forth at pages 145 - 152 of the present specification and discussed below that the claimed compositions of the present invention have been **effective in treating the effects of HIV infection, including weight loss, KS lesions and $CD4^+$ T cell counts.**

Further the Office states that:

> "The language of the claims is not strictly limited to *in vitro* treatments and encompasses treating infected patients and as such does not have support in the specification. There is insufficient disclosure to reasonably predict that the methods and compositions of the instant specification would inhibit HIV infection or replication *in vivo*."

As stated above, applicants have amended the independent claims to recite a composition and method for treating the effects of HIV infection and applicants have provided sufficient tests results in the present application to show the efficacy of the claimed compositions and methods in both human test subjects and a large animal model. For example, as discussed at pages 145 - 152 of the present application, the compositions of the present invention were tested on SIV infected male rhesus monkeys and human patients infected with HIV and in both animal models were found effective in treating the effects of the respective virus.

The effectiveness of the same fractions that were prescreened for anti-viral and anti-KS activity (*in vitro*), were studied in five adult male rhesus monkeys who were intravenously inoculated with cell free SIV_{mac251} ($10^{4.5}$ $TCID_{50}$/ml). In all animals, SIV p27 was apparent in plasma 14 days after infection, reaching a maximum by about day 20. Treatment with systemic injections (3,000 IU, 2 times weekly) of the preparation of hCG (APL^{TM}), was initiated 3 weeks after SIV inoculation. Two months post-inoculation, the characteristic increase of SIV p27 antigen (Figure 2A), reduction of $CD4^+$ T cells

(Figure 2B), and weight loss (Figure 2C) occurred in 2 of 2 untreated infected monkeys. In contrast, the 3 infected monkeys treated with the hCG preparation showed weight gain characteristic of uninfected animals of this age (Figure 2C), a marked decrease in SIV p27 (Figure 2A) and an increase in $CD4^+$ T cells to normal levels (Figure 2B). These effects were maintained over the 7 months the animals were followed. These results show that the compositions of the present invention can treat the effects of SIV by increasing $CD4^+$ T cells and promoting weight gain in SIV infected rhesus monkeys.

Test results in human clinical trials also show that the presently claimed compositions are effective in treating the effects of HIV infection including, weight loss, KS lesions and $CD4^+$ T cell counts. A total of 47 patients were enrolled under protocols of compassionate use sanctioned by the Institutional Review Boards of the respective centers. 29 patients were treated in Belgium, either on a protocol to investigate intralesional and systemic treatment of cutaneous KS (n=15), or in the pre-clinical phase of that protocol (n=4), or on compassionate use for systemic KS or HIV infection (n=10). The protocol involved intralesional administration of 500 IU hCG (PREGNYL™) to 4 lesions for 2 weeks, followed by subcutaneous administration of 2,500 IU hCG (PREGNYL™) 5 days per week for 4 to 6 weeks.

A total of 18 patients were treated in California with at least 1 month of follow-up as part of an ongoing protocol to evaluate systemic hCG therapy for cutaneous KS. These patients received either 5000 IU of APL™ subcutaneously 7 days per week, 10,000 IU subcutaneously 3 times per week, or 10,000 IU subcutaneously 7 days per week.

Thirty-six patients survived the study, 7 died either from opportunistic infections or multiple organ failure. The vital status of 1 patient is unknown. Two patients discontinued hCG treatment because of cholestasis. Among the 30 cases with cutaneous Kaposi's Sarcoma, 12 were treated with intralesional followed by systemic therapy in Belgium and 18 with systemic therapy only in California. Among 8 patients with both visceral and cutaneous KS treated in Belgium with very advanced pulmonary or gastric lesions, 3 patients experienced complete remissions, 2 patients exhibited tumor stabilization and 3 progressed, in each case after failure of conventional cytotoxic therapy.

AIDS patients treated with hCG therapy were tested for increases in $CD4^+$ T cell levels (in numbers of cells per mm^3) and decrease in viral load by one of the following assays for determining viral load: NASBA (Louache, et al., 1992, *Blood* 180:2991-2999; Geller, et al., 1985, *Archs. Path. Lab. Met.* 109:138-145), which has a lower detection limit of 4,000 copies; Roche Amplicor, with a lower detection

limit of 200 copies; RT-PCR, with a lower detection limit of 100 copies; or TCID assay in which the infection of PBMCs in co-culture is determined (Popovic et al., 1984, *Science* 204:497-500).

Among the 22 patients with analyzable $CD4^+$ T cell data, 5 demonstrated a pro-$CD4^+$ T cell effect (PH-VE, PH-RF, PG-9, PG-17, and PG-19) characterized by a 50% rise in $CD4^+$ T cell count sustained over at least a one month period, as demonstrated by plotting the data from at least two patients (PH-VE--Figures 3G and H and PG-17--Figures 3I and J). Of these 5 patients, concomitant stable non protease anti-virals were administered to 2 patients, stable protease inhibitors in 2 cases and hCG preparation alone in 1 case. Thus of the 6 cases with valid $CD4^+$ T cell data on hCG preparation alone, 1 manifested a significant response. No patient experienced an adverse fall in $CD4^+$ T cell on hCG preparation therapy, although patient PH-VE experienced an 0.7 log rise in viral load with a sustained 50% fall in $CD4^+$ T cell numbers and a partial anti KS response (Figures 3G and H). Similarly, patient PG-17 experienced a significant rise in $CD4^+$ T cells and no change in viral load on hCG therapy alone, yet experienced progression of KS after 2.5 months (Figures 3I and J).

Among the 26 patients analyzable for weight gain (patients who started hCG preparation therapy coincident with or shortly after starting other anti-viral therapy were excluded), 14 gained weight, 3 experienced weight loss, and 9 remained stable. There was no correlation between weight change and dosage of hCG, however, there was a pattern observed in some patients where an initial weight gain was followed by a return to baseline levels while others experienced sustained weight gain over several months.

Thus, applicants have shown that hCG therapy was well tolerated clinically by patients and there was no evidence for an adverse effect of hCG on viral load or $CD4^+$ T cell level. Further, applicants have shown that the claimed compositions of the present invention were effective in increasing or at least maintaining weight gain and $CD4^+$ T cell counts and reducing lesions due to systemic KS in patients infected with HIV.

The Office also rejected claims 40, 42-44, 82 and 84-86 under 35 USC §112, first paragraph because the Office contends that the specification while enabling for the composition extracted from urine does not reasonably provide enablement for all "native sources." Applicants disagree but to move prosecution of the application forward, applicants have amended the claims to recite that the compositions are extracted from urine.

Applicants have shown the efficacy of the presently claimed compositions in both humans and rhesus monkeys, and as such, respectfully request that all rejections under 35 USC §101 and §112, first paragraph be withdrawn.

Conclusion

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Stucker reconsider the patentability of all composition and method claims, in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Stucker is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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